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Cross-coupling reaction of thermally stable titanium(π)-alkyne complexes with aryl halides catalysed by a nickel complex

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The first cross-coupling reaction of thermally stable titaniu- $m(\pi)$ -alkyne complexes with aryl iodides in the presence of a catalytic amount of Ni(cod)₂ is presented.

Alkyne–metal complexes prepared from low-valent early transition metal compounds such as Ti(II), Zr(II), Nb(III), and Ta(III) are very useful synthetic reagents since they are known to function as 1,2-dicarboanionic olefins.^{1–4} Nonmetallocene (η^2 -alkyne)Ti(O-*i*-Pr)₂ is an especially versatile synthetic reagent and a wide variety of reactions have been explored by Sato and coworkers.^{1,5} However, the Ti(II)–alkyne complexes thus obtained are thermally unstable and can only be used below -30 °C.

On the other hand, much less attention has been paid to Ti compounds as substrates in transition metal catalysed reactions.⁶ It is well-known that the transition metal catalysed cross-coupling reaction of organic halides with Mg, B, Sn, and Si compounds is one of the most straightforward methods for C–C bond formation.⁷ However, there is only one example of the cross-coupling reaction using a Ti compounds, in which thermally stable Ti(rv) compounds such as MeTi(O-*i*-Pr)₃ and PhTi(O-*i*-Pr)₃ were employed as substrates.⁸

Quite recently, Eisch and coworkers reported that $Ti(\pi)$ alkyne complexes prepared from alkynes and $Bu_2Ti(O-i-Pr)_2$ generated from $Ti(O-i-Pr)_4$ and BuLi at -78 °C were thermally stable at 25 °C.⁹ Their work prompted us to report our independent finding that thermally stable $Ti(\pi)$ -alkyne complexes can be utilized as substrates in transition metal catalysed reactions. In this communication, we report an unprecedented transition metal catalysed cross-coupling reaction of $Ti(\pi)$ alkyne complexes with aryl halides. The $Ti(\pi)$ complexes were stable even at 50 °C and Ni catalysed reaction afforded coupling products in good yields.

Thermally-stable Ti(π)–alkyne complexes (1) were successfully generated by slow addition of 2 equiv. of *n*-BuLi as a reducing reagent (for the Ti(π) to Ti(π) process) to a mixture of Ti(O-*i*-Pr)₄ and alkyne in THF at -78 °C followed by raising the temperature to 50 °C (eqn. 1).

Then, the THF solution of **1** was stirred for an additional hour at 50 °C prior to further reaction. The formation of diphenylacetylene complex (**1a**) was verified by hydrolysis or deuteriolysis of the reaction mixture affording *cis*-stilbene or *cis*-stilbene- d_2 (>98% D) in almost quantitative yield (entry 1, Table 1). As for the reducing reagent, *n*-BuLi is appropriate to stabilize the Ti(π)-alkyne complex at 50 °C. The use of *s*-BuLi also works similarly as judged by the formation of *cis*-stilbene in high yield (95%) after the hydrolysis. However, other reducing reagents affect the thermal stability of **1** considerably: **1a** prepared with *i*-PrMgBr or *n*-BuMgBr *in lieu* of *n*-BuLi was not stable and afforded *cis*-stilbene in quite low yield (~ 20%) after hydrolysis at 50 °C. As for a titanium compound, when TiCl₂(O-*i*-Pr)₂ or Ti(O-*t*-Bu)₄ was employed instead of Ti(O-*i*- Pr)₄ in entry 1 (Table 1), **1** was not so stable and the yield of *cis*stilbene was less than 50%. Thus, the Ti(O-*i*-Pr)₄–*n*-BuLi– alkyne system is suitable for generation of the thermally stable **1**. Various thermally stable Ti(π)–alkyne complexes (**1b**–**f**) were successfully generated as evidenced by the excellent yields of **2** after hydrolysis at 50 °C (entries 2–6, Table 1).

For further evaluation of the thermal stability of 1, the allylation reaction of 1 with allylic bromides (3) at 50 °C was carried out (eqn. 2, Table 2).



In contrast to previous monoallylation reactions of **1** with **3** at low temperature (-50 °C, then warmed up to rt),¹⁰ the reaction of **1a** with allyl bromide (**3a**) at 50 °C afforded diallylation product (**4a**) as a major product in high yield (99% yield and 90% selectivity, entry 1, Table 2). The allylation reactions with crotyl bromide (**3b**) and methallyl bromide (**3c**) similarly gave diallylation products as major product (entries 2 and 3, Table 2). The higher reaction temperature (50 °C) would favor the diallylation reaction.

Since the Ti(π)–alkyne complexes (1) are thermally stable at 50 °C, 1 may be utilized as substrates even in a transition metal

Table 1 Hydrolysis of thermally stable Ti(II)-alkyne complexes $(1)^a$

Entry	\mathbb{R}^1	R ²		Yield of 2^{b} (%)
1	Ph	Ph	1a	99
2	p-CH ₃ C ₆ H ₄	p-CH ₃ C ₆ H ₄	1b	97
3	Ph	(CH ₃)Si	1c	92
4	Ph	Me	1d	90
5	<i>n</i> -Pr	<i>n</i> -Pr	1e	95
6	(CH ₃) ₃ Si	(CH ₃) ₃ Si	1f	95

^{*a*} Conditions: alkyne (0.50 mmol), Ti(O-*i*-Pr)₄ (0.50 mmol), *n*-BuLi (1.0 mmol as 1.6 M hexane solution) and THF (3.0 mL) at -78 °C, then warmed up to 50 °C. ^{*b*} GLC yields determined by the internal standard method.

Table 2 Allylation of Ti(n)-alkyne complex (1a) with allylic bromides $(3)^a$

Entry	R ³	R ⁴		Yield (%) (4 : 5) ^{<i>b</i>}
1	H	H	3a	99 (90 ^c : 10 ^c)
2	Me	H	3b	87 (77 ^d : 23 ^e)
3	H	Me	3c	77 (65 ^c : 35 ^e)

^{*a*} Conditions: **1a** (0.50 mmol), **3** (2.0 mmol) and THF (3.0 mL) at 50 °C for 24 h. ^{*b*} GLC yields determined by the internal standard method. ^{*c*} E : Z = 2 : 8. ^{*d*} E : Z = 1 : 9. ^{*e*} E : Z = 1 : 1.

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catalysed reaction carried out above room temperature. Among possible reactions, a cross-coupling reaction was chosen, and 1 was reacted with aryl iodide (6) in the presence of a nickel catalyst (eqn. 3).

$$1 + Ar-I \xrightarrow{\text{Cat}} B = R + BR + BR + BR + C = CHAr + ArC = CHAr + ArC = CHAr + ArC = CHAr + CAR + CA$$

Ni(cod)₂ showed the highest catalytic activity and crosscoupling products (7a and 8a) were afforded in 81% total yield from 1a and 4-iodobenzotrifluoride (6a) at 50 °C with 5 mol% of the nickel complex (entry 1, Table 3).† Other nickel or palladium catalyst precursors such as Ni(acac)₂, Pd(OAc)₂, and Pd(PPh₃)₄ only showed poor catalytic activity. The catalyst loading slightly affected the reaction: iodobenzene (6b) afforded the products in 60, 65, and 75% yields with 10, 40, and 100 mol% of Ni(cod)₂, (entries 2-4, Table 3). 3-Iodobenzotrifluoride (6c) and 1-fluoro-4-iodobenzene (6d) afforded the corresponding products in moderate yields (entries 5 and 6). As for aryl halides, iodides gave the best results, whereas the corresponding bromides, chlorides, and triflates afforded low yields (< 10%). Other Ti(II) complexes of di-*p*-tolylacetylene (1b), 4-octyne (1e), and 3-hexyne (1g) also provided the corresponding coupling products in moderate to high yields (entries 7-9, Table 3).

Although all attempts to isolate or fully characterize 1 were unsuccessful, we measured the ¹³C NMR spectrum of **1a** in THF- d_8 (0.3 M). In the aliphatic region of the spectrum, two peaks at 28.4 and 72.6 ppm were assignable to methyl and methine carbons of the *i*-Pr group, respectively. These two

Table 3 Nickel-complex catalysed cross-coupling reaction of Ti(II)-alkyne complexes (1) with aryl iodides $(6)^a$

Entry	$\mathbf{R} (= \mathbf{R}^1 = \mathbf{R}^2)$	Ar	Yield (%) (7 : 8) ^{<i>b</i>,<i>c</i>}
1	Ph (1a)	<i>p</i> -CF ₃ C ₆ H ₄ (6a)	81 (74 ^d : 26 ^e) (7a : 8a)
2^{f}	1a	Ph (6b)	60 (65 : 35) (7b : 8b)
3 ^g	1a	6b	65 (55 : 45) (7b : 8b)
4^h	1a	6b	75 (40 : 60) (7b : 8b)
5	1a	$m-CF_{3}C_{6}H_{4}$ (6c)	55 (89 ^{<i>i</i>} : 11 ^{<i>e</i>}) (7c : 8c)
6	1a	$p-FC_{6}H_{4}$ (6d)	$40 (90^e : 10^e) (7d : 8d)$
7	<i>p</i> -CH ₃ C ₆ H ₄ (1b)	6a	72 (79 ^d : 21 ^e) (7e : 8e)
8	<i>n</i> -Pr (1e)	6a	48 (84 ⁱ : 16 ^e) (7f : 8f)
9	Et (1g)	6d	41 (93 ^d : 7 ^e) (7g : 8g)

^a Conditions: 1 (0.50 mmol), 6 (2.0 mmol), Ni(cod)₂ (0.025 mmol, 5 mol%), and THF (3.0 mL) at 50 °C for 24 h. b GLC yields determined by the internal standard method. ^c In addition to the coupling products, 3,6-dihydro-2,2,4-trimethyl-5,6-diphenyl-2H-pyran was obtained (5-20%) in entries 1–6: ¹H NMR (CDCl₃) δ 1.42 (s, 3H), 1.48 (s, 3H), 1.60 (s, 3H), 1.93 (d, J = 15 Hz, 1H), 2.56 (d, J = 16 Hz, 1H), 5.25 (s, 1H), 6.76 (d, J = 4 Hz, 2H), 7.08-7.18 (m, 8 H); ¹³C NMR (CDCl₃) δ 21.2 (CH₃), 23.6 (CH₃), 30.9 (CH₃), 42.4 (CH₂), 71.4 (C), 78.1 (CH), 126.1 (CH), 126.6 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 129.4 (CH), 133.6 (C), 139.3 (C), 141.3 (C); HRMS (EI) calc. for C₂₀H₂₂O: m/z 278.1671. Found: m/z 278.1666. Anal. calc. for C20H22O: C, 86.29; H, 7.97. Found: C, 85.99, H, 7.88%. $^{d}E: Z = 4: 6. ^{e}E: Z = 1: 1. ^{f} Ni(cod)_{2}$ (0.050 mmol, 10 mol%). ^g Ni(cod)₂ (0.20 mmol, 40 mol%). ^h Ni(cod)₂ (0.50 mmol, 100 mol%). ⁱ E : Z = 3 : 7.

resonances were not consistent with the *i*-Pr carbons of *i*-PrOLi (30.6 and 64.4 ppm) and Ti $(O-i-Pr)_4$ (26.8 and 76.6 ppm) in the same solvent and at the same concentration. This result might suggest that 1 did not exist as a simple mixture of $(\eta^2 - \eta^2)$ alkyne)Ti(O-*i*-Pr)₂ and *i*-PrOLi, but was obtained as an ate-type complex¹¹ such as $[(\eta^2 - alkyne)Ti(O - i - Pr)_4]^2 - 2Li^+$, which might cause the thermal stability of 1. Further study on the structure and thermal stability of 1 is currently in progress.

Notes and references

† A mixture of diphenylacetylene (89 mg, 0.50 mmol), Ti(O-i-Pr)₄ (115 mg, 0.50 mmol) and THF (3.0 mL) was placed with a magnetic stirring bar in a 20 mL round-bottomed flask under an argon flow. The mixture was cooled to -78 °C and n-BuLi (1.0 mmol, 1.6 M solution in hexane) was added dropwise over 5 min. Then, the reaction mixture was slowly warmed to 50 °C over 1 h and stirred at the same temperature for an additional hour. To this solution, 6a (544 mg, 2.0 mmol) and Ni(cod)₂ (7 mg, 0.025 mmol) were added and the reaction mixture was stirred at 50 °C for 24 h. After the reaction, the whole mixture was passed through a short silica gel column to afford a clear vellow solution. GLC and GC-MS analyses of the reaction mixture showed the formation of the cross-coupling products (7a and 8a)12 in 81% yield. Isolation of the cross-coupling products for NMR analysis was carried out by column chromatography (silica gel with hexane/CH2Cl2, 95/5).

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